

**Immune regulation of herpes simplex virus type 2 infection:
Special emphasis on the transcription factor T-bet**

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att försvaras offentligt i Föreläsningssalen, våning 3, Guldhedsgatan 10A, Göteborg

Fredagen den 19 januari 2007 kl. 09:00

av
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Avhandlingen baseras på följande arbeten:

- I. **Alexandra Svensson, Inger Nordström, Jia-Bin Sun, Kristina Eriksson.**
Protective immunity to HSV-2 infection is mediated by T-bet.
Journal of Immunology 2005 174:6266-6273
- II. **Alexandra Svensson, Niklas Björkström, Ann-Marie Bergin, Gun-Britt Löwhagen, Petra Tunbäck, Lars Bellner, Peter Horal, Hans-Gustaf Ljunggren, Leonid Padyukov, Kristina Eriksson.**
A 3'-UTR polymorphism in TBX21 (T-bet) gene is a risk factor for genital HSV-2 infection in humans.
Submitted for publication
- III. **Alexandra Svensson, Lars Bellner, Mattias Magnusson, Kristina Eriksson.**
Role of IFN- α/β signaling in the prevention of genital herpes virus type 2 infection.
Journal of Reproductive Immunology 2007 in press
- IV. **Alexandra Svensson, Joanna Kaim Carina Mallard, Annika Olsson, Ernst Brodin, Tomas Hökfelt, Kristina Eriksson.**
Neurokinin 1 receptor (NK1R) signaling affects the local innate immune defense against genital herpes virus infection.
Journal of Immunology 2005 175:6802-6811

Immune regulation of herpes simplex virus type 2 infection: Special emphasize on the transcription factor T-bet

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Herpes simplex virus type 2 (HSV-2) is a sexually transmitted pathogen that infects the genital tract mucosa as well as local sensory neurons. It is the most common cause of genital ulcer disease in humans. The infection gives rise to a wide range of symptoms, ranging from severe and painful recurrent episodes of genital herpes to silent infection. The overall aim of this thesis was to evaluate the contribution of different innate and acquired immune mediators to the incidence, severity, prevention and treatment of HSV-2 infection. For this purpose I used a mouse model of genital HSV-2 infection, to assess how different signaling pathways affect innate and acquired protection to HSV-2. In parallel, blood samples from symptomatic and asymptomatic HSV-2-infected individuals and from healthy uninfected individuals were screened for possible genetic risk factors for HSV-2 susceptibility and disease. I found that the neuropeptide Substance P had anti-viral properties. Using different gene-targeted mice I found that the receptor for substance P (the neurokinin 1 receptor, NK1R), as well as the transcription factor T-bet and the receptor for IFN-alpha/beta are required for innate protection against HSV-2. These factors influence different pathways in the anti-viral response; both T-bet and NK1R were required for the adequate function of NK cells, whereas the IFN alpha/beta receptor signaling pathway was necessary for the induction of type I interferons. IFN-alpha/beta receptor signaling was also required for efficient anti-viral treatments that utilize ligands for different Toll-like receptors. Furthermore, acquired immunity to HSV-2 was impaired in T-bet-deficient (but not in NK1R- or IFN-alpha/beta receptor-deficient) animals and was associated with reduced vaccine-induced CD4⁺ T cell responses and reduced IFN-gamma production. Finally, I identified a HSV-2 susceptibility locus in the human T-bet gene. The allelic distribution of this gene differed significantly between HSV-2-infected individuals and healthy controls, but not between asymptomatic and symptomatic HSV-2-infected patients. No functional effect has yet been linked to this polymorphism, although I show that it affects neither NK cell numbers/phenotype nor T-cell numbers and their IFN-gamma production. In conclusion, I describe the transcription factor T-bet, the cytokine family of type I interferons and the neuropeptide substance P, which in various ways contribute to the immune regulation of HSV-2 infection. Understanding the signaling mechanisms involved in HSV-2 infection may facilitate the development of novel preventive and therapeutic treatments for genital herpes infection.

Key words: Herpes simplex virus type 2, T-bet, Substance P, Neurokinin 1, IFN- α/β signaling, polymorphisms

ISBN 91-628-7036-X